Pain monitor: reality or fantasy in ambulatory patients

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Purpose of review
In an unconscious patient, there can be significant challenges to monitoring nociception and proper dosing of analgesic medications. The traditional measures of intraoperative nociception have poor sensitivity and specificity with little predictive value in postoperative outcomes such as postoperative pain, opioid-induced side effects, length of stay or incidence of opioid use disorder. To date, several monitoring modalities are in development to establish objective measures of the balance between nociception and analgesia with the goal of guiding anesthesiologists and improve patient outcomes. In this review, some of the most promising monitoring modalities are discussed with the most recent findings.

Recent findings
Multiple modalities are beginning to demonstrate utility compared with traditional care. Most, but not all, of these studies show decreased intraoperative opioid use and some show lower pain scores and opioid requirements in the postanesthesia care unit.

Summary
Recent evidence points to promising efficacy for these monitoring modalities; however, this field is in its infancy. More investigation is required to demonstrate differences in outcome compared with traditional care, and these differences need to be of sufficient import to achieve widespread adoption.

Keywords
ambulatory surgery, analgesic guidance, nociception-analgesia balance, pain monitoring

General anesthesia encompasses a reversible state of unconsciousness, amnesia, akathisia and analgesia [1]. While the pain sensation is an unpleasant experience associated with actual or potential tissue injury, this complex subjective experience results from activation of a distributed brain network, referred to as the pain matrix, with sensory-discriminatory and affective-cognitive-evaluative neuroanatomical components [2]. The challenges with monitoring the state of analgesia have been well known, especially with the use of muscle relaxation [3], and the current practice involves the utilization of short-acting opioid analgesics to contribute to the anesthetic state, but the effects of opioids can be influenced by various pharmacokinetic/pharmacodynamic variables that can invariably increase the risk of overdosing or underdosing [4]. More than 75% of surgical procedures are conducted in ambulatory setting with better patient satisfaction at lower costs [5,6]. For successful ambulatory surgery, specific complications that could result in delay in discharge or readmission have to be addressed including pain and postoperative nausea and vomiting (PONV) [7].

To achieve adequate depth of analgesia, the balance of nociception and antinociception must be accurately assessed and used to guide analgesic administration, however, the most common approach of utilizing autonomic reactions such as tachycardia, hypertension or sweating under general anesthesia are unreliable [8]. The ideal nociception monitor for ambulatory procedures must be responsive, reliable, robust, well correlated with administration of analgesics or degree of surgical stimulation, demonstrate cost effectiveness and clinical utility with specific focus on reducing PONV and postoperative pain. In the last decade, several promising monitoring modalities have been introduced to clinical practice with surrogate variables to

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KEY POINTS

- Multiple approaches are being developed to improve information about nociceptive/antinociceptive balance during surgery.
- Utility of monitoring nociceptive state may extend to postoperative period with potential for improving long-term outcomes.
- Multiple utility studies are needed to demonstrate if and how these monitors may improve anesthetic care and patient outcomes.
- Additional studies are needed to understand how drugs acting on the sympathetic nervous system can influence data provided by these monitors.

estimate this nociception–antinociception balance and support clinical decision making in analgesic administration. Such variables are derived from electroencephalography (EEG), electromyography (EMG), plethysmography, heart-rate (HR) variability (HRV), skin conductance or central reflexes such as pupillometry, as discussed below.

SURGICAL PLETHYSMOGRAPHIC INDEX

The Surgical Plethysmographic Index (SPI, GE Healthcare, Helsinki, Finland) represents an evaluated measure of nociceptive–antinociceptive balance that combines metrics based on photoplethysmographic pulse wave amplitude (PPGA) and the normalized heartbeat interval (HBI). Investigators originally demonstrated the suppression of PPGA and variability in HBI during propofol–remifentanil anesthesia, as a reflection of sympathetic response, correlated with the intensity of stimulus and the remifentanil effect site concentration (C_e) [9]. SPI ranges from 0 to 100 with values of 20 to 50 representing adequate balance of nociception–antinociception intraoperatively. The lower SPI values indicate low surgical stress response (analgesic state) and high SPI represents high stress (nociception).

Various studies have been conducted to evaluate the clinical utility of SPI, with mixed results. For example, it was demonstrated in ambulatory surgery patients that SPI-guided care resulted in lower remifentanil and propofol administration and faster awakening compared with control patients [10]. However, in a study under sufentanil-sevoflurane general anesthesia, SPI guided care provided no significant benefit [11]. Significantly, a recent meta-analysis that included both studies, reported that SPI-guided care resulted in lower opioid administration and faster time to extubation compared with control patients [12▪]. A recent study in trauma patients demonstrated that opioid consumption as well as need for vasopressor administration were reduced utilizing a combination of entropy and SPI guidance compared with standard of care [13▪▪]. A recent study described that in patients undergoing laparoscopic cholecystectomy, fentanyl administration guided by SPI compared with guidance by hemodynamic changes resulted in higher intraoperative fentanyl consumption in SPI group, but better pain control and less opioid administration in the postoperative period [14▪].

The SPI may have a role in predicting the degree of postoperative pain. An SPI of greater than 30 during the last 10 min of surgery had a positive predictive value of almost 90% in identifying patients that would have moderate or severe pain in their early postanesthesia care unit (PACU) course [15]. It should be noted that several clinical circumstances and confounders affect autonomic variables that are at the core of SPI. Administration of vagolytics or cardiac pacing [16], fluid challenge [17] or placement of patients in steep Trendelenburg or reverse Trendelenburg position [18] can significantly alter SPI. Absent these issues, SPI does appear to have utility in guiding opioid administration, but more investigation is required to ascertain the current recommended 'ideal' index value of 20–50 which should be modified depending on the intended outcome improvement, such as decreased intraoperative opioid administration or lower postoperative pain scores.

PUPILLOMETRY

The pupils dilate in response to noxious stimulation, and this pupillary dilatation reflex (PDR) increases with increased stimulation and is blunted with opioids [19]. In clinical studies, there are indications of the potential utility of pupillometry. Elevated PDR prior to tracheal suctioning of deeply sedation ICU patients predicted those who would be excessively stimulated by the procedure [20]. In the immediate postoperative period, PDR was highly correlated with pain scores and with the amount of morphine subsequently required to achieve patient comfort [21]. In either setting, it would be interesting to study the utility of opioid titration protocols based on PDR findings to improve patient care.

Other pupillary characteristics may have utility as well. Measuring the minute fluctuations in pupillary diameter, or 'pupillary unrest' in postoperative patients identified patients who would have successful improvement in pain scores with opioid treatment [22]. In an intraoperative protocol, Sabourdin

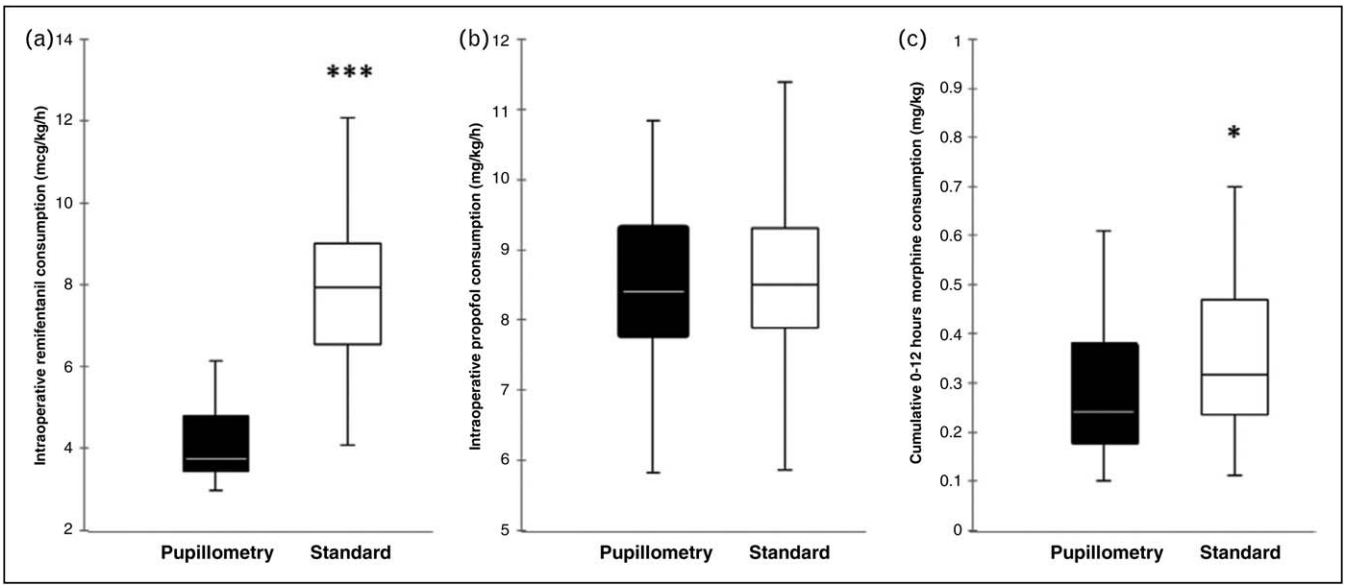

FIGURE 1. Pupillometry-guided care and opioid administration. Compared with conventional care, pupillometry-guided care resulted in less remifentanil administration (panel a) and 12-h postoperative morphine administration (panel c) with no difference in propofol administration (panel b). Boxes: median (25–75th percentile), $^{*}P < 0.05$, $^{***}P < 0.001$. Adapted with permission [23▪▪].

et al. [23▪▪] titrated remifentanil to the difference between ongoing pupil size compared with baseline measurement. When the diameter of pupil was greater than 30% above baseline, remifentanil was increased, when 5% or less above baseline, it was decreased, and if between 5 and 30% of baseline, no changes were made. Compared with a control group, the titration group received significantly less remifentanil, required significantly less morphine in the postoperative period (Fig. 1), and, perhaps most interesting, had less chronic pain at 3 months. While this study requires confirmation, it suggests that there may be a connection between intraoperative opioid use and long-term outcomes, and that pupillometric-guided opioid titration may improve long-term outcomes.

There are further challenges to the use of pupillometry. One is technical, requiring access to the eyes. Moreover, it is a procedure requiring periodic human intervention and is not a continuous measure. Further PDR is a function of response to a noxious stimulation, usually delivered by tetanic stimulation, but this stimulation is not standardized. More work needs to be done to delineate the effect of age, as demonstrated by the need for higher sevoflurane concentrations to suppress the PDR for skin incision in prepubertal compared with postpubertal children [24]. Furthermore, when the degree of stimulation and opioid level are held constant, PDR is less robust at deeper propofol-induced hypnotic state [bispectral index (BIS) of 25] compared with a lighter state (BIS of 50) [25▪]. This speaks to the complex interaction of level of stimulation, hypnotic state and antinociceptive state on the PDR. Despite these limitations, pupillometry shows clear promise and deserves further evaluation. Several devices are available for monitoring the pupils that can perform PDR such as AlgiScan (IDMed, Marseille, France) but there is no evidence to suggest superiority of one over others.

NOCICEPTION FLEXION REFLEX

The nociception flexion reflex (NFR), also known as RIII-reflex, is a spinal withdrawal reflex and has found utility in monitoring responsiveness to noxious stimulation. Currently, the Paintracker (Dolosys, Berlin, Germany) is a commercially available monitor utilizing NFR. To deduce the nociceptive threshold, standardized electrical stimuli are applied to the ipsilateral sural nerve and electromyographic activity of the biceps femoris muscle recorded [26]. This NFR threshold is increased with administration of analgesics or absence of noxious stimulation, with potential ability to predict movement in response to noxious stimuli. A recent study demonstrated the predictive value of NFRS during emergence on postoperative pain [27▪]. Nevertheless, to date, all the studies are limited by small numbers and variability in methodology. Further studies are warranted to demonstrate clinical utility of this monitoring technique.

HEART RATE VARIABILITY

Respiration causes subtle changes in the R–R interval of the electrocardiogram. This HRV can be analyzed for information about the relative activity of the sympathetic and parasympathetic nervous system. The analgesia nociception index (ANI, PhysioDoloris, MetroDoloris, Lille, France) focuses on the HRV from 0.15 to 0.40 Hz, which is considered the high-frequency spectrum of HRV, and is associated with parasympathetic nervous system activity [26]. This monitor produces a dimensionless score of 0–100 representing the degree of parasympathetic tone. As a result, high ANI (>70) correlates with high parasympathetic activity or a low stress state, representing antinociception, and a low ANI (<50) represents states of nociception [28]. This monitor is designed to show both an 'instantaneous' value and one averaged over the previous 4 min. The monitor requires the patient to be in sinus rhythm and parasympathomimetic drugs (atropine etc.) should be avoided.

Multiple experimental and observational studies demonstrate that, under general anesthesia, ANI responds to noxious stimulation as well as the administration of opioids. In an experimental protocol, electrical stimulation significantly decreased ANI and these decreases were blunted with increased levels of remifentanil [29]. A recent observational study in neurosurgical patients demonstrated that ANI correlated well with hemodynamic changes and responded to fentanyl administration [30▪]. Similarly, recent observational studies in children found ANI to respond to skin incision and to fentanyl administration, particularly when fentanyl was given while ANI was below 50 [31▪,32▪].

Several recent studies have described using the ANI to guide opioid administration. In a study of vascular surgery patients, Daccache, Caspersen [33] utilized a remifentanil target control infusion to maintain an ANI between 50 and 70. Despite absence of a control group, enrolled patients required very low remifentanil administration rates and good clinical outcomes, however, 11% of patients experienced a somatic reaction, such as coughing, which may be prohibitive in other types of surgery. In a protocol in bariatric surgery patients, ANI-guided care resulted in less sufentanil administration compared with historic controls [34▪]. There were no outcome differences between the groups, but the study was small and underpowered to detect them.

Two prospective randomized utility studies have been published. In a protocol of intraoperative morphine administration during laparoscopic cholecystectomy, no difference was found between the ANI-guided and the control groups in the amount of morphine administration, the time below ANI of 50, or in other outcome measure [35]. In the discussion, the authors speculated that the study design, using a 'slow acting' opioid and titrating to the 4-min averaged ANI may have contributed to the lack of a difference between the groups. In another study of patients undergoing lumbar laminectomy, ANI-guided fentanyl titration resulted in significantly lower pain scores and opioid usage in the PACU compared with control patients [36▪▪]. Significantly, the total amount of intraoperative fentanyl was equivalent, but in the ANI-guided group, it was administered earlier in the procedures, more contemporaneous with the acute surgical stimulation, suggesting that the outcome improvement may have come from better matching of opioid to nociception (Fig. 2).

There may be utility in ANI-guided general anesthesia in predicting a patient's degree of postoperative pain. An ANI of less than 50 just prior to emergence was demonstrated to have high sensitivity, specificity and negative predictive value for the subsequent report of moderate-to-severe postoperative pain [37]. Following emergence, the utility of ANI to predict postoperative pain is less clear with some studies showing a positive association [38] while others do not [39]. Perhaps these differences are due to differences in study design, surgical procedures or anesthetic techniques.

A recent study [40▪] compared analgesic guidance by SPI, ANI or anesthesiologists' judgment (control) with a sufentanil bolus protocol. They failed to see any difference among the groups in postoperative cortisol levels, time to spontaneous breathing at the end of anesthesia and postoperative pain scores, but they noted that sufentanil boluses were delivered significantly earlier in both monitored groups, suggesting better matching of opioid administration to nociception.

Changes in the ANI are associated with nociception and the administration of opioid analgesics. More investigation is needed to understand whether patient outcomes can be improved with its utilization.

MULTIPARAMETER APPROACH

The nociception level index (NOL, Medasense, Ramat Gan, Israel) utilizes a multiparametric approach and includes HR, HRV, pulse plethysmography, skin conductance and fluctuations in skin conductance with their time derivatives [41]. It is a dimensionless score of 0–100 developed through forest regression intended to be a combined index of stimulus intensity and analgesia. Multiple observational protocols have demonstrated that higher NOL Index values are associated with increasing

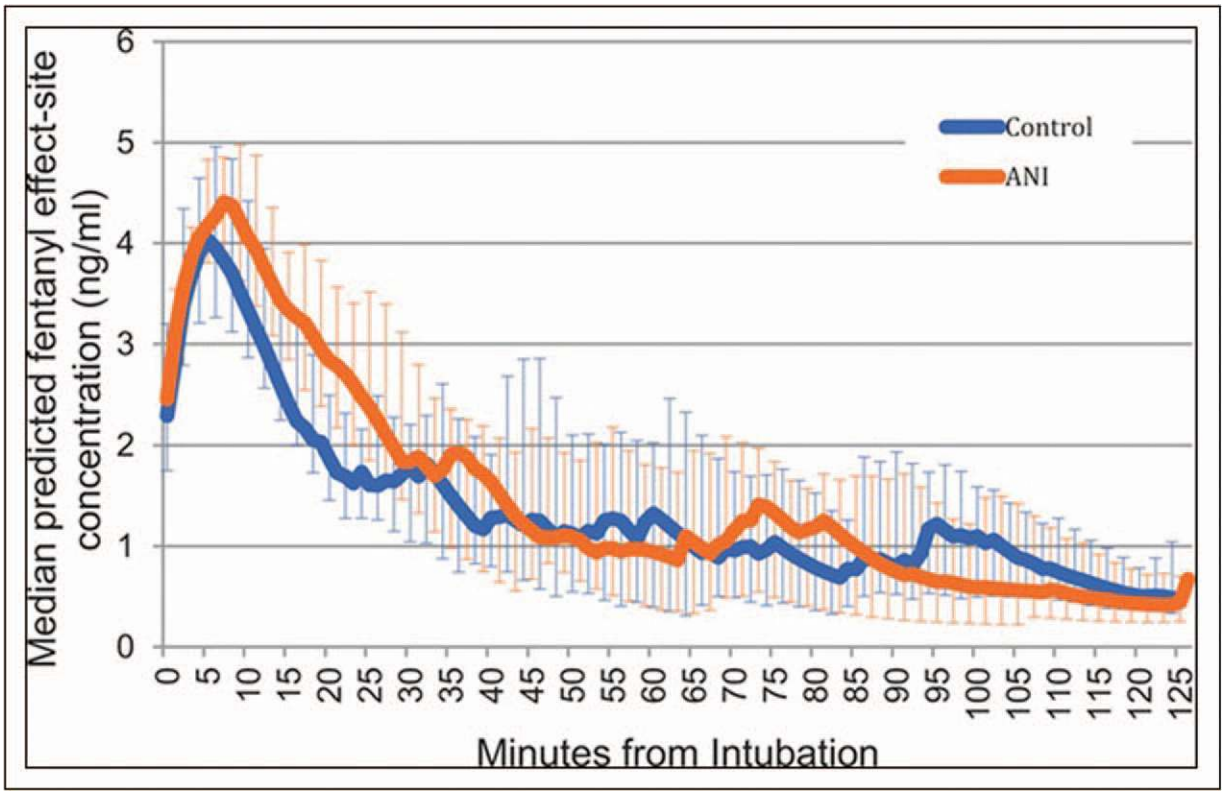

FIGURE 2. Analgesia nociception index-guided care and opioid administration. During spine surgery, analgesia nociception index-guided care resulted in lower pain scores and fentanyl administration in the postanesthesia care unit compared with conventional care. However, total intraoperative fentanyl was not different between the groups. The graph demonstrates that the predicted fentanyl effect-site concentration in the analgesia nociception index-guided group was greater (27%) early in the surgery during the most nociceptive periods of the procedure. This suggests that the monitor's benefit may come from more accurately matching opioid administration and nociception compared with conventional care. Adapted with permission [36▪▪].

nociception and that opioid analgesics blunt noxious stimulation-induced increases in the index value. In a protocol utilizing propofol and remifentanil, NOL index outperformed HR and mean arterial blood pressure (MAP) in differentiating intubation and skin incision from nonnoxious stimuli, showed graded decrease in response to stimulation with increasing levels of opioid and, in the nonstimulated state, was not affected by remifentanil level [42]. Another observational protocol compared the NOL with HR, pulse plethysmograph amplitude, MAP and SPI and demonstrated that the NOL index correlated with intensity of noxious stimuli and remained unchanged in response to nonnoxious stimulation [43]. They also demonstrated that compared with other measures of nociception, NOL was able to better discriminate noxious from nonnoxious stimulation with a high degree of sensitivity and specificity, and it was able to reflect two different analgesic concentrations of remifentanil during periods of noxious stimulation. A third protocol compared NOL index with HR, MAP, BIS and ANI in patients with epidural analgesia under remifentanil-desflurane anesthesia and demonstrated that tetanic stimulation resulted in increased NOL index, while increasing doses of remifentanil resulted in progressively lower increases in NOL values with stimulation, and that both NOL and ANI outperformed traditional methods of assessing nociception [44▪]. Another similar recent study of patients under remifentanil-desflurane anesthesia with epidural analgesia demonstrated high sensitivity and specificity of NOL index in discriminating noxious from nonnoxious stimulation [45▪].

These observational studies describe the NOL threshold value with the greatest combination of sensitivity and specificity to differentiate between periods of noxious stimulation and no stimulation, describing values of 16 [42], 15 [41] and 10 [45▪]. These differences are probably due to study design, but they may identify the value, below which, further analgesia may not have utility during noxious stimulation. Indeed, a recent protocol compared NOL-guided remifentanil target-controlled infusion to standard of care during BIS-guided propofol

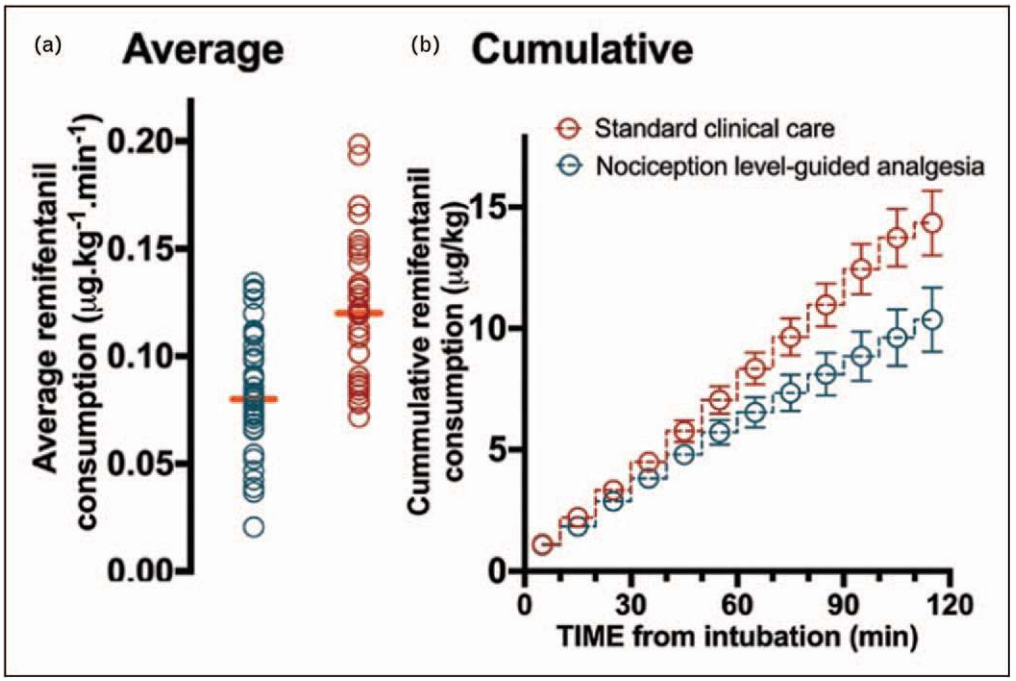

FIGURE 3. Nociception level-guided care and opioid administration. Nociception level-guided remifentanil target-controlled infusion resulted in significantly less remifentanil administration compared with traditional care during major abdominal, urologic or gynecologic surgery. Panel (a) shows individual remifentanil doses (μg/kg/min) and mean values (orange bars) $P < 0.001$. Panel (b) shows cumulative remifentanil administration over the first 2 h. Adapted with permission [46▪▪].

anesthesia [46▪▪]. In the NOL-guided group the remifentanil target was adjusted to maintain a NOL between 10 and 25 by making adjustments of 0.5 ng/ml every five minutes. In the control group remifentanil adjustments were based on traditional parameters. The NOL-guided patients received 30% less remifentanil (Fig. 3), required fewer vasoactive medications and emerged, on average, 2 min faster than the control patients, all significant findings. There were no differences in postoperative pain scores or opioid requirement, but the study was not powered for these secondary outcomes.

ELECTROENCEPHALOGRAPHY-PARAMETER APPROACH

The qCON monitor [qCON 2000 Monitor; Quantium Medical (Fresenius Kabi), Mataro, Spain] reports two values of qCON and qNOX. qCON is a measure of depth of anesthesia and correlates with similar technology such as BIS. The qNOX is a dimensionless score (0–99) derived from a proprietary algorithm utilizing an adaptive neuro fuzzy inference system utilizing EEG and EMG signals. A qNOX score of less than 40 predicts very low likelihood, 40–60 low likelihood, and above 60 high likelihood of movement in response to a noxious stimulus [47]. An observational study showed that qNOX and qCON scores changed independently in response to various stimulation suggesting that they monitor different dimensions [48]. In addition, the prestimulation qNOX value was predictive of movement to laryngeal mask airway insertion. To date, there are no clinical studies investigating the utility of qNOX in clinical setting.

FURTHER CONSIDERATIONS

None of the monitors discussed approved have been approved by the United States Food and Drug Administration (FDA) for use as a monitor of nociception. The ANI monitor has been approved by the FDA as a HRV monitor and is marketed as the high frequency variability index monitor. In addition, as most of these monitors are measuring variables associated with the sympathetic nervous system, more study is needed to understand how drugs that affect the sympathetic nervous system influence their function and utility.

CONCLUSION

The practice of titrating opioid and nonopioid analgesics has not significantly changed since the advent of balanced anesthesia care. Clinicians continue to rely on signs and symptoms of autonomic nervous system stimulation or depression. The monitors described in this review have been developed with the intention of improving this practice,

especially due to low sensitivity and specificity of traditional measures of analgesia such as tachycardia, hypertension or sweating. The studies done so far offer significant proof of concept and some early utility information. Ultimately, for these monitors to enter routine anesthetic care, further studies need to be done to demonstrate better outcomes compared with 'standard care'. In addition, these improved outcomes need to be of enough significance to lead to change in practice. Improvements such as reduced opioid usage, improved postoperative analgesia, reduced postoperative opioid use disorder or reduced PONV could lead to the incorporation of these monitors in clinical practice. It is conceivable that these benefits may be more difficult to demonstrate in ambulatory surgery, given the less invasive nature of ambulatory procedures, but until the appropriate studies are conducted, this cannot be determined.

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Conflicts of interest

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